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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
16051-9US CC/

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]	Application Number	Filed
	10/661,088	09/12/2003
on _____	First Named Inventor	
Signature _____	Andrew VAILLANT et al.	
	Art Unit	Examiner
Typed or printed name _____	1648	PENG, Bo

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- [ ] applicant/inventor.
- [ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- [X] attorney or agent of record. Registration number 47,352
- [ ] attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

/Christian Cawthorn/
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CHRISTIAN CAWTHORN
Typed or printed name
514-847-4256
Telephone number
04/18/2008
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

- [X] *Total of 3 forms are submitted.

File No. 16051-9US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Andrew VAILLANT et al.
Serial number:	10/661,088
Filing date:	September 12, 2003
For:	ANTIVIRAL OLIGONUCLEOTIDES TARGETING HBV
Art Unit:	1648
Examiner:	Bo, PENG
Agent:	Christian CAWTHORN

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
U. S. A.

Sir:

Please find enclosed herewith form PTO/SB/33 for the pre-appeal brief request for review. Please consider the reasons below for which the review is being requested.

A Notice of Appeal is being filed concurrently. This response is being filed concurrently with a petition for a three-month extension of time.

Claims 39-41 are pending in the application.

REASONS

Claim rejections - 35 U.S.C. § 103

Claim 40 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Pan et al. in view of Davis *et al.*

In this regard, the Examiner notes that Pan *et al.* teach the "construction of a library of 87-nt oligonucleotides that contain random 40-nt (40N) at a central region..." The Examiner also notes that Pan *et al.* suggest modifications to RNA chain, which is a call of trial or testing with other modifications such as phophorothioate oligonucleotides. In this regard, first of all, as previously noted, the random sequences used by Pan *et al.* are only the starting material used for screening. Such screening could not have been made or else it would not be a screening if not practiced on random sequences. However, at the end of the 12 rounds of amplifications and selections made, the material used by Pan *et al.* for testing for anti-RSV activity is no more a pool of random sequences, but specific sequences that they were able to select, clone and sequence (see from page 11511, last paragraph to page 11512, second complete paragraph.

Furthermore, REP 2006 is a non-selected (or non-isolated) pool of oligonucleotides, which, if following the teaching of Pan et al, would not have predicted to have any antiviral activity. In fact, Pan et al. teaches that specific active oligonucleotides must be selected using a selection (12 rounds of selection) method from a RNA pool. However, it is clear in Pan *et al.* that the RNA pool (random sequence, see page 11511, as discussed below) is not active.

Furthermore, Pan et al. demonstrates only the uses of RNA oligonucleotides as potential inhibitors of viruses. Indeed, in the 12 rounds of amplification, they select RNA oligonucleotides by contacting a RNA pool with RSV. The amplified pool or specific clones are always in the form of RNA for testing the antiviral activity as clearly shown in Figure 1. REP 2006 is DNA (oligodeoxynucleotide) with phosphorothioate modification. Thus one skilled in the art would have been led to believe that it only applies to RNA having antiviral effect and would not have thought of combining it with Davis *et al.*, which describes specific DNA sequences.

Moreover, Pan et al. note at page 11511, lines 5-6 of the first paragraph that "the presence of random-sequence RNA molecules at 330 nM had no effect". Furthermore, the Applicants respectfully submit that indeed Pan *et al.* suggest some type of modifications for developing RNA analogs, but readily notes at page 11512, right column, about mid page, that the analog pool was 7-

10 times less effective in neutralizing RSV. The RNA analogs of random sequences at 200 nM had no effect on RSV infection." The authors goes even further in stating "it was likely that the lower anti-RSV activity of the RNA analogs was due to the RNA structural changes induced by the 2'-fluoro modification in pyrimidines", clearly suggesting unpredictability of activity with RNA analogs differently modified. However, it is clear from the specification as a whole and even more from the various passage quoted above, that Pan *et al.* are not considering a random sequence, but only specific sequences, and that modifications on RNA are making predictions of anti-RSV activity impossible. Clearly Pan *et al.* is teaching away from the present invention. Therefore, Pan *et al.* not only are they not teaching random oligonucleotides sequences with anti-RSV, let alone HBV, activity, but Pan *et al.* also do not teach or predict the effect of modifications, such as phophorothioated oligonucleotides on the anti-RSV activity.

It is respectfully submitted that such missing teaching from Pan *et al.* is not found in Davis *et al.* Nowhere in Davis *et al.* is there any teaching of random oligonucleotides having anti-HBV activity. In fact, Davis et al. is teaching the stimulation of the immune system with their product, whereas the Applicants sought in developing the present invention to lower toxicity and interaction with the immune system (see paragraph [00161]) When the Applicants wanted to stimulate the immune system, they suggest indeed at paragraph [00185] to couple the antiviral non-specific sequence, as now claimed, with "...CpG, Gquartet, and/or CG that are described in the literature as stimulators of the immune system". From the passage at paragraph [00185] that the Applicants never intended, and are not even now, claiming CpG motif. There is a clear distinction made between the non-specific sequence (random) of the invention and the motifs such as CpG. The claims as now on file do not include the recitation of inclusion of "motifs", and thus the claimed random oligonucleotides do not include CpG motif, as these were made distinct and are not recited in the claims. The claims on file are now limited to a random sequence, i.e. a non-specific sequence, oligonucleotide, without recitation of motif sequences as defined by the Applicants at paragraph [00185]. Thus, even if Davis *et al.* report anti-HBV activity with specific motif sequences, the deficiencies noted from Pan *et al.* are still missing, i.e. at least for the random oligonucleotides and

the phosphorotioation of random oligonucleotides on anti-HBV activity. No prediction is possible as taught by Pan *et al.*

In light of the above and foregoing, since both references when combined do not teach the entire invention as now claimed, reconsideration and withdrawal of the Examiner's rejection is respectfully solicited.

Claim 40 has also been rejected under 35 U.S.C. 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. 103 as being obvious over Davis *et al.*

The Examiner is alleging that the property must have been inherent to the oligonucleotide, to reverse the burden on the Applicants. To allege that the composition claimed is inherently the same as that disclosed by the reference, the Examiner must be able to allege that the composition from the reference is the same as that claimed. However, in light of the differences noted above, it is clear for one skilled in the art upon reading the claim that the two compositions are not the same, namely the composition of the present invention does not include "motifs", such as CpG. As evidenced above, such motifs were considered distinct by the Applicants from the random oligonucleotides (see paragraph [00185]. Therefore, the Examiner did not meet the burden of proof that the two compositions are the same. Also mentioned above, the intent of the Applicants was not to stimulate the immune system, but to lower the toxicity of the oligonucleotides and to reduce the interaction with the immune system (see paragraph [00161]). It was made clear at paragraph [00161] that the goal of using random oligonucleotide was to lower toxicity. It was known that "different sequences may trigger different responses in the animal, such as general toxicity, interaction with serum proteins, and interaction with immune system" As described and claimed by the Applicants, [t]he mixture of ONs may thus decrease toxic effects because the level of any particular sequence will be very low, so that no significant interaction due to sequence or nucleotide composition is likely. From the above, it is clear that the Applicants intended to reduce any interaction with the immune system. Moreover, at paragraph [00185], motifs, such as CpG and others, have been referred to distinctively from the non-specific sequence oligonucleotides of the present invention. Should the applicants have

intended that the oligonucleotides contains some of those motifs, said motifs would either need not to be referred to separately or distinctively from the oligonucleotides of the present invention, or would need to specifically mention in the claims that the composition also contains CpG motifs, neither of which possibilities the claims encompass. Reading the claims to have them include CpG motifs would amount to do the opposite of the aim announced at paragraph [00161]. Such reading or interpretation is thus not possible.

Accordingly, since the Applicants is claiming a composition that is different from the point of view of its constituting elements from the composition of Davis *et al.*(no motifs in the composition of the present invention), a 102/103 rejection alleging inherency is improper. Reconsideration and withdrawal of the Examiner's rejection is earnestly solicited.

It is submitted, therefore, that the claims are now in condition for allowance. Reconsideration of the Examiner's rejections is respectfully requested. Allowance of claims 39-41 at an early date is solicited. Should the case be returned to the Examiner for resolution of minor issues left, the Examiner is earnestly solicited to call the undersigned to discuss any outstanding issues.

Respectfully,

Date: April 18, 2008

By: /Christian Cawthorn/
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